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10/581,172	02/06/2007	Mara Rossi	SER-109	3915

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EXAMINER	
BORGEEST, CHRISTINA M	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,172	ROSSI, MARA	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22,25 and 26* is/are pending in the application.

4a) Of the above claim(s) *25 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,17 and 22* is/are rejected.

7)☒ Claim(s) *15, 16 and 18-21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-22) in the reply filed on 12 January 2009 is acknowledged. Claims 25-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12 January 2009.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Objections

Claims 1, 6, 8-11, 13-15, 21, 22 are objected to because of the following informalities:

(i) Claims 1 and 22 use the acronym "FSH" without first defining what it represents in the independent claims. While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym.

(ii) In claim 22, line 7, the term "ff" should be capitalized.

(iii) Claims 6, 8-11, 13-15, 18, 21 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other

multiple dependent claim. See MPEP § 608.01(n).

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3- 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(i) Claims 3-22 are rejected as being indefinite because claims 3, 8, 13, 17, 19 and 22 contain the trademark/trade name Sepharose. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe ion exchange, metal ion and hydrophobic interaction chromatography and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3 and 6-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolfenson et al. (INSTITUTO MASSONE S.A., published 26 October 2000—on Applicants' 1449 form) in view of Chiba et al. (Endocrine J. 44; 205-218, 1997—on Applicants' 1449 form). The claims recite methods for purifying recombinant human follicle stimulating hormone (FSH) or an FSH variant comprising the steps of subjecting FSH to (1) ion exchange chromatography; (2) immobilised metal ion chromatography; and (3) hydrophobic interaction chromatography (HIC). In deciding whether claims are obvious under 35 U.S.C. 103(a), the first factor to consider is to determine the scope and contents of the prior art. Wolfenson et al. teach purification of gonadotropins using a scheme outlined on the title page that comprises two ion exchange chromatography steps followed by two hydrophobic interaction chromatography (HIC) steps. Wolfenson

et al. describe at p. 9 (whole page) that the ion exchange chromatography can be carried out with a strong anion exchange resin and suggest the use of the Q Sepharose and that the HIC can be carried out using the Phenyl-Sepharose resin (see also claims 3 and 4).

The second factor to consider is to ascertain the differences between the prior art and the claims at issue. Wolfenson et al. do not teach a further purification step using immobilized metal ion chromatography (note that metal ion chromatography is a type of affinity chromatography). Chiba et al. teach purification of FSH using affinity chromatography followed by immobilized metal ion affinity chromatography and HIC (see p. 207, whole page). Chiba et al. further teach that the metal ion affinity chromatography is carried out with a resin having tridentate chelating groups that are iminodiacetic acid and Cu^{2+} (see p. 207, left column, 1st paragraph). Chiba et al. also teach that the metal ion chromatography is carried out with a resin having similar properties to chelating Sepharose FF, as evidenced by p. 6, lines 5-10 of their description, which outline conditions similar to those described at p. 207, left column, 1st paragraph (e.g., tridentate chelate groups such as iminodiacetic acid and Cu^{2+}). Note that claims 11 and 12 recite that the metal ion chromatography eluted with ammonium acetate at a pH of at or about 9 and claim 14 recites that the HIC is eluted with ammonium acetate (50 mM)/ammonium sulfate(0.25M). Although neither of the references teach these precise conditions, they do teach these buffers as eluents. Wolfenson et al. teach about 50mM ammonium acetate (pH 7) as an eluent for ionic exchange chromatography. Wolfenson et al. teach 0.4 - 1.2 M ammonium sulfate as an

eluant for HIC at p. 9, 1st paragraph. Chiba et al. teach also teach ammonium sulfate (1.7M) as an eluent for HIC at p. 207, left column last paragraph through right column, 1st paragraph. Note also that claim 12 recites "at or about a pH of 9", therefore, a pH of 7 can reasonably be interpreted as "at or about." Given that the recited buffers are standard buffers used in chromatography and that choice of buffers can be optimized as part of routine experimentation (i.e., no undue burden is placed on one of ordinary skill in the art to optimize conditions), the differences in buffers and concentration recited in these claims are not enough to support patentability. See MPEP 2144.05:

A. Optimization Within Prior Art Conditions or Through Routine Experimentation

> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Wolfenson et al. by adding a step using metal ion chromatography in the purification scheme, as taught in Chiba et al. because Chiba et al. identified a shortcoming of ion exchange chromatography that was recognized in the art at the time, namely, that it cannot achieve complete separation of gonadotropins because of charge heterogeneity (see p. 205, right column). Thus Chiba et al. proposed a purification scheme using affinity chromatography followed by metal ion affinity chromatography and HIC in order to remedy the problem. The person of ordinary skill in the art would have been motivated to combine the teachings for several reasons. First, Chiba et al. identified for the person of ordinary skill in the art the limitations of the well known method of ion exchange chromatography, thus the artisan had guidance as to the problem, as well as a possible solution. Second, one of ordinary skill in the art would have been motivated to combine purification schemes to prepare a purer FSH product. FSH is used in treatment of infertility, and there is strong motivation in the art to have pure product in treatment regimens, as outlined in the first 3 pages of Wolfenson et al. Third, in protein purification, there are a finite number of predictable methods in order to achieve a result, namely, ion exchange chromatography, HIC and affinity chromatography. Wolfenson et al. teach ion exchange chromatography (2 steps) and HIC (2 steps) and Chiba et al. teach affinity chromatography (2 steps) and HIC (2 steps). Wolfenson et al. also teach that the steps can be performed in any order at p. 7, 2nd paragraph:

> The steps described in the present invention can be used following in a different order from the one herein described, which does not imply

> varying the invention philosophy. Equally satisfactory results were obtained by inserting, for example, the hydrophobic interaction resin between the two ionic exchange chromatography steps described later.

Thus the person of ordinary skill in the art had guidance as to the ability to optimize the purification schemes. The claims recite methods comprising, thus are encompass purification schemes using other types of chromatography not recited in the claims (such as Concanavalin A affinity chromatography described at p. 206, right column, 2nd paragraph by Chiba et al.) Given the guidance of Wolfenson et al. and Chiba et al., it would be well within the level of ordinary skill in the art of protein purification to pursue the known options to devise a scheme comprising ion exchange chromatography, metal ion affinity chromatography and HIC (i.e., optimization). As outlined above, there are only a finite number of types of chromatography in the protein purification art, and the person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. Furthermore, the claims recite "comprising", thus encompass additional steps not specifically recited in the claims. There is also no evidence in the specification of the criticality of the recited buffers as eluents. Furthermore, the person of ordinary skill in the art could have reasonably expected success because the skill in the art of protein purification is high and optimization of methods is the norm. If a person of ordinary skill in the art pursues the known options within his or her technical grasp and this leads to success, it is likely the product not of innovation but of ordinary skill and common sense. Thus the claims do not contribute anything non-obvious over the prior art.

Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolfenson et al. (cited above) in view of Chiba et al. (cited above) as applied to claims 1-3 and 6-14 above, and further in view of Tikhomirov et al., Journal of chromatography, 1978: 167: 197-203. The explanation as to why claims 1-3, 6-10 and 13 are rendered obvious by Wolfenson et al. and Chiba et al. is applicable here and is hereby incorporated into this rejection. Claims 4-5 recite methods of claim 1 wherein the ion exchange chromatography is carried out using borate buffer as eluent, wherein the borate buffer is at a pH of at or about 8.5. Neither Wolfenson et al. nor Chiba et al. suggest borate buffer at or about a pH of 8.5 as an eluent for ion exchange chromatography. Tikhormirov et al. teach borate buffer as an eluent at a pH of about 8.5 in a procedure to separate and determine amino acids, amino sugars and neutral carbohydrates (see abstract; p. 200, Table I). In the abstract they teach "[s]tepwise elution systems with sodium citrate and borate buffers have developed for the ion-exchange liquid chromatographic separation of amino acids and sugars...With the aid of this system, the direct quantitative comparison of sugars and amino acids by liquid chromatography becomes possible for the first time." Tikhomirov et al. teach further at p. 202, last paragraph: "Fig. 3 shows a chromatogram of 7.8 μg of a hydrosylate of ovalbumin that was optimized especially for the elucidation of the sugar content in glycoproteins. The DA-X-808-column was reduced in size to 65x4mm. For isocratic elution a 0.5 M boric acid buffer [i.e., borate buffer] of pH 8.5 was used..." Their teachings illustrate the high level of skill in the art (i.e., the ability of the person of ordinary skill to optimize conditions) and that they developed a method that was ideal

for glycoproteins, which contain sugars and amino acids. There is also no evidence in the specification of the criticality of the use of borate buffer at or about a pH of 8.5 as an eluent. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the combined teachings of Wolfenson et al. and Chiba et al by using borate buffer at a pH of 8.5, as taught in Tikhomirov et al. because Tikhomirov et al. teach a chromatographic method that was optimized for glycoproteins. For this reason as well, the person of ordinary skill in the art would have been motivated to make the substitution. Furthermore, the person of ordinary skill in the art could have reasonably expected success because of the high skill in the art, evidenced by the ability of the ordinarily skilled artisan to optimize conditions and the findings of Tikhomirov et al., who teach a chromatographic method that was optimized for glycoproteins, the type of protein to which FSH belongs. Thus the claims do not contribute anything non-obvious over the prior art.

Closest Prior Art

Claims 15 and its dependents, 16 and 17 are drawn to an additional step in the purification scheme to be carried out in a particular order. Note claim 15: the method of claim 1, comprising a second step of ion exchange chromatography (2a), carried out ***after*** the step of immobilised metal ion chromatography, and ***before*** the step of hydrophobic interaction chromatography (HIC). (Emphasis added by Examiner). Note also claim 18 and its dependents, 19-21 are drawn to an additional step in the purification scheme to be carried out in a particular order: 18. The method of claim 1,

further comprising a step of reverse phase chromatography (4), carried out ***after*** the step of hydrophobic interaction chromatography (HIC). (Emphasis added by Examiner). Although Wolfenson et al. teach two steps of ion exchange chromatography, they do not teach that this step occurs after metal ion chromatography, and nothing taught by Chiba et al. remedies this. Neither of the cited references teach an additional phase of reverse phase chromatography to be conducted after HIC. Paradisi et al. (US Patent Publication 20030186893, published 2 October 2003) discloses a purification scheme for LH in which ion-exchange chromatography and the reverse phase HPLC are performed twice (see abstract) and reverse phase HPLC is performed after ion-exchange chromatography (see claim 2). Although Wolfenson et al. suggest that the order in which the steps are performed is not important, claim 2 of Paradisi et al. recites a particular order: A process according to claim 1 comprising the steps of: (a) subjecting the sample to ion-exchange chromatography to produce a ***first*** eluate; (b) subjecting the ***first*** eluate to reverse phase HPLC, to produce a ***second*** eluate; and (c) subjecting the second eluate to gel permeation chromatography. (Emphasis added by Examiner). Thus Paradisi et al. do not teach or suggest the same level of optimization as taught by Wolfenson et al., who state at p. 7, 2nd paragraph that the disclosed steps can be performed in any order. In addition, the purification methods recited in instant claims 1-14 encompass being performed in any order. However, claims 15-21 introduce steps that are to be performed in a particular order and the cited prior art does not teach or suggest the recited order. Finally claim 22 is recited in such a manner that the particular order is maintained:

> A method for purifying human recombinant FSH comprising the steps of subjecting FSH to: (i) ultrafiltration; (ii) anion exchange chromatography on Q Sepharose FF with at or about 50 mM borate, at or about 0.13 M NaCl, pH at or about 8.5 as eluent; (iii) ***subjecting the eluate of step (ii) to a step*** of immobilised metal ion affinity chromatography on chelating Sepharose ff, with Cu.sup.++ as metal ion, and at or about 0.75 M ammonium acetate pH at or about 9 as eluent; (iv) ***subjecting the eluate of step (iii) to a step*** of anion exchange chromatography on DEAE Sepharose FF, with at or about 0.11 M Ammonium acetate, pH at or about 8.5 as eluent; (v) ***subjecting the eluate of step (iv) to a step*** of hydrophobic interaction chromatography on Phenyl Sepharose FF HS with at or about 50 mM ammonium acetate, at or about 0.25 M ammonium sulphate, pH at or about 8.25 as eluent; (vi) ***subjecting the eluate of step (v) to a step*** of reverse phase chromatography on Source 30 RPC, with at or about 50 mM ammonium acetate, pH at or about 7.6, with at or about 20% of 2-propanol (v/v); (vii) ***subjecting the eluate of step (vi) to a step*** of ultrafiltration; and (viii) subjecting the retentate of step (vii) to a step of nanofiltration. (Emphasis added by Examiner).

Given the recitation of the steps in a particular order, claims 15-22 are free of the art.

Conclusion

Claims 1-22 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is (571)272-4482. The examiner can normally be reached on 9:00am - 3:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Bridget E Bunner/

Primary Examiner, Art Unit 1647